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10/594,453	09/26/2006	Michael Kretschmar	LNK-019	1342

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EXAMINER	
TSAY, MARSHA M	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,453	KRETSCHMAR ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-8,10-15,17 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4-8,10-15,17 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/04/10; 01/21/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received January 4, 2010.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 1, 3, 9, 16, 18-23 are canceled. Claims 2, 4-8, 10-15, 17, 24 are currently under examination.

Priority: The request for priority to GERMANY 102004044429.3, filed September 14, 2004, is acknowledged.

Objections and Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 4-6, 8, 10-14, 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. (US 4341764; previously cited) in view of Newman et al. (US 5710254; previously cited). For examination purposes, even though claim 2 uses closed claim language "consisting of", the steps of 2(ii) and 2(iii) have been given their broadest and most reasonable interpretation, i.e. one *or more* steps can be encompassed by "removing" and "treating", since steps 2(ii) and 2(iii) do not require a *specific* sub-step or sub-steps for "removing" the fibronectin precipitate in step 2(ii) or for "treating" the composition in step 2(iii). That the "adjusting",

"removing", and "treating" steps of claim 2 encompass one *or more sub-steps* is supported by claim 6, which recites recited the open-ended term "comprises" in the phrase, "wherein removing step (ii) *comprises* stirring the plasma fraction" (emphasis added).

Wallace et al. disclose a method for preparing fibronectin and antihemophilic factor from blood plasma comprising the steps of: forming a solution of blood plasma fraction in an aqueous medium, acidifying the solution to a pH sufficient to form an acid precipitate, separating the acid-precipitate from the solution, isolating fibronectin from the precipitate, and isolating antihemophilic factor from the solution at a temperature of 2°-20° C (col. 9-10 lines 1-21; claims 2, 4-5, 24). Wallace et al. further disclose that the solution can be acidified at a pH of about 5.0 to form the acid precipitate (col. 9 line 13; claims 2, 4-5). Wallace et al. also disclose the plasma fraction is dissolved cryoprecipitate (col. 9 line 9, col. 5 line 28; claim 14). In Example 1, Wallace et al. disclose the acid precipitate contains 260 g protein in 13 liters of a buffer (col. 5 line 34; claim 8). After precipitation, the precipitate suspension was stirred for 3 hours (col. 5 lines 50-53; claim 6). In col. 4, lines 40-42, Wallace et al. disclose that the precipitate contains a major proportion of the fibronectin (i.e. greater than 50%, preferably greater than 60%). Wallace et al. do not expressly disclose that by practicing the disclosed method, a precipitate is formed and removed, where the precipitate comprises 70-90% of the initial amount of fibronenctin. It is known in the art that cryoprecipitated plasma fractions are prepared with suitable buffers in order to purify out coagulation factors. Even so, Wallace et al. do not expressly teach initial concentrations of NaCl or glycine.

Newman et al. disclose that a cryoprecipitate can be prepared from normal human plasma where said cryoprecipitate has an initial concentration of 60 mM glycine and 40 mM NaCl prior to treatment to obtain vWF (von Willebrand factor). See column 2, lines 29-31.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to separate fibronectin and/or a coagulation factor from a plasma fraction by the method of Wallace et al. as noted above and such that the major proportion of the fibronectin precipitate is composed of fibronectin, (i.e. greater than 60%, 70%, etc.), as well as to add the sodium-glycine buffer of Newman et al. into the initial preparation of the cryoprecipitate of Wallace et al. (claims 2, 4-6, 8, 10-14, 24). Since Wallace et al. disclose that the percentage of fibronectin in said precipitate is preferably greater than 60%, it would be reasonable for one of ordinary skill to accept that said fibronectin precipitate of Wallace et al. can contain up to 70%, 80%, and even 90% of fibronectin since the range of greater than 60% is disclosed. Further, in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) (The prior art taught carbon monoxide concentrations of "about 1-5%" while the claim was limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5% thus the ranges overlapped.)". Similarly, a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

Regarding the motivation to add the sodium-glycine buffer of Newman et al., the motivation would be to obtain an initial plasma fraction preparation that will yield the most stable environment and preserve the activity of the blood factors that one of ordinary skill would like to purify (claims 10-13). See also the paragraph above regarding the case where the instant ranges "overlap or lie inside ranges disclosed by the prior art."

In their remarks, Applicants assert that (1) while it is true that the temperature range disclosed in Wallace et al. overlaps with that of the present claims at the specific value of 20° , when one considers the reference as a whole, it becomes clear that the claimed combination is neither taught nor suggested by Wallace et al. Wallace et al. suggest that the disclosed process is performed at a pH ranging from 5.0 to 6.95, more preferably about 6.5 to 6.95, using a solution chilled to a temperature of about 2°-20° C, preferably about 2.5°-7.5° C (col. 2: 37-40, emphasis added). Wallace et al. later suggest that the disclosed processes may be used to obtain a yield of "greater than 50%", preferably "greater than 60%" of the fibronectin (col. 4: 41-42). One of skill in the art, in considering these two sections together, would readily expect that only use of the more preferred conditions (i.e., pH of 6.5 to 6.95 and temperature of 2.5°-7.5°C) would give rise to the more preferred yield of "greater than 60%". The skilled artisan would likewise expect that any deviation from these preferred conditions (e.g., pH of 5.3 and temperature of 20°C) would give rise to a lesser yield (i.e., less than 60%, more likely less than 50%). Accordingly, Applicants respectfully submit that the presently claimed process, including a process temperature of 20°C to 25 °C, a process pH between 4.7 and 5.3, and a fibronectin yield of 70% to 99%, cannot be fairly characterized as obvious in view of Wallace et al. (2) Applicants also

point to a comparison of Fig. 1 and 2 of Wallace et al. This confirms Applicants' position that Wallace suggests (a) towards a two-step process and (b) away from a one-step acid-precipitate process such as that presently claimed, which together give rise to an expectation that the process as presently claimed would be less effective, providing a yield of less than the preferred 60% and more likely less than 50% -- certainly well below the 70% to 99% fibronectin recovery required by the pending claims. (3) On the issue of overlapping ranges, Applicants wish to remind the Examiner that a presumption of obviousness may be rebutted by showing that (a) the prior art teaches away from the claimed invention, or (b) the invention provides new and unexpected results relative to the prior art. *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.,* 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004). In this case, Applicants respectfully submit that both (a) and (b) are true. With regard to the former, as noted above, Wallace teaches away from the combination of claimed parameters, particularly the combination of a single acid-precipitate step performed at 20°C or higher, as a means for improving fibronectin recovery. With regard to the latter, Applicants have clearly demonstrated that fibronectin removal is most efficient at room temperature (e.g., 20°C), in contrast to the prior art suggestions that cold temperatures are required. See Table 2 of Applicants' specification. Applicants respectfully submit that the unexpected superior results obtained could not have been predicted by one of ordinary skill in the art, particularly in view of the teachings of Wallace that clearly suggest towards the combination acid-chill procedure, and thus serve as further indicia of non-obviousness. (4) Newman et al. disclose a suspended cryoprecipitate containing 60 mM glycine and 40 mM sodium chloride at pH 7. This is clearly outside the range required by the instant claims, which set a minimum sodium chloride concentration at 100 mM.

Applicant's arguments have been fully considered but they are not persuasive.

(1) Response: As explained in the beginning of the instant 103(a) rejection, even though claim 2 uses closed claim language "consisting of", the steps of 2(ii) and 2(iii) have been given its broadest and most reasonable interpretation, i.e. multiple steps can be encompassed by "removing" and "treating", since steps 2(ii) and 2(iii) do not recite how the fibronectin precipitate is "removed" in step 2(ii) and how the composition is "treated" in step 2(iii).

Applicants are also reminded that "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In this instance, while Wallace et al. may suggest preferred ranges (i.e. pH 6.5 to 6.95 and a temperature of 2.5°-7.5°C) within the larger range of pH 5.0 to 6.95 and a temperature of 2°-20°C, it does not criticize, discredit or teach away from the larger range of pH 5.0 to 6.95 and a temperature of 2°-20°C, which is within the scope of the instant pH 4.7 to 5.3 and temperature of 20°-25°C. Wallace et al. *expressly* disclose that the acid-chill precipitate can be at a pH 5.0-6.95 and at temperature of about 2°-20° C (col. 7 line 65 to col. 8 line 2), which overlaps with the instantly recited range of 20° C to 25° C and pH 4.7-5.3. As such, by practicing the method of Wallace et al. at 20°C and pH 5.0, which is expressly taught by the reference, the desired percentage of fibronectin in the precipitate would have been achieved. Moreover, because Wallace et al. acknowledge that greater than 60% fibronectin can be achieved by practicing the method at a temperature including 20°C and pH 5.0, the resulting percentage of fibronectin removed would not be unexpected.

(2) Response: It should be noted again that "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Since Wallace et al. *expressly* disclose that the acid-chill precipitate can be at a pH 5.0-6.95 and at temperature of about 2°-20° C (col. 7 line 65 to col. 8 line 2), which overlaps with the instantly recited range of 20° C to 25° C and pH 4.7-5.3. As such, by practicing the method of Wallace et al. at 20°C and pH 5.0, which is expressly taught by the reference, the desired percentage of fibronectin in the precipitate would have been achieved. Moreover, because Wallace et al. acknowledge that greater than 60% fibronectin can be achieved by practicing the method at a temperature including 20°C and pH 5.0, the resulting percentage of fibronectin removed would not be unexpected.

Regarding Applicants' remarks that Wallace et al. teach a two-step acid-chill precipitate process, which is different than the instant one-step acid-precipitate process, it should be noted that instant claim 2 recites that steps (i) and (ii) are performed at a temperature that ranges from 20° to 25°C and step (ii) recites a pH 4.7 to 5.3. Therefore, the instant process is also an acid-chill precipitate process where the change in pH and temperature is performed at the same time. Therefore, the instant step is within the scope of Wallace et al. since Wallace et al. also disclose acidifying and chilling the blood plasma fraction to obtain a precipitate (col. 7 lines 44-50).

(3) Response: Regarding Applicants' remarks that Wallace et al. teach away from the combination of claimed parameters, see the response of (1) and (2).

Regarding Applicants' remarks that Applicants have clearly demonstrated that fibronectin removal is most efficient at room temperature (i.e. 20°C), it should be noted that Wallace et al. also disclose a temperature of 20°C. See the 103(a) rejection above, as well as the responses for (1) and (2).

Regarding Applicants' remarks of unexpected results (Table 2 of Applicants' specification), since Wallace et al. *expressly* disclose that the acid-chill precipitate can be at a pH 5.0-6.95 and at temperature of about 2°-20° C (col. 7 line 65 to col. 8 line 2), which overlaps with the instantly recited range of 20° C to 25° C and pH 4.7-5.3. As such, by practicing the method of Wallace et al. at 20°C and pH 5.0, which is expressly taught by the reference, the desired percentage of fibronectin in the precipitate would have been achieved. Moreover, because Wallace et al. acknowledge that greater than 60% fibronectin can be achieved by practicing the method at a temperature including 20°C and pH 5.0, the resulting percentage of fibronectin removed would not be unexpected.

(4) Response: It should be noted that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already

generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.").

In this instance, Wallace et al. disclose the instant pH and temperature parameters. Newman et al. is used as a 103(a) reference to remedy the deficiency of Wallace et al. to disclose a sodium-glycine buffer. However, since Newman et al. disclose the general conditions of a cryoprecipitate prior to treatment to obtain vWF (i.e. 60 mM glycine and 40 mM sodium chloride at pH 7), it would be reasonable for one of ordinary skill to determine at which concentration of NaCl can be added to an initial preparation of cryoprecipitate to preserve the activity of the blood factors that one of ordinary skill would like to purify (instant claim 2).

The same reasoning applies for dependent claims 10-13, regarding the glycine concentration.

For at least these reasons, the instant claims are rejected under 103(a) as being unpatentable over Wallace et al. in view of Newman et al.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. (US 4341764; previously cited) in view of Newman et al. (US 5710254; previously cited). The teachings of Wallace et al. in view of Newman et al. are outlined above. Wallace et al. disclose the acid-precipitate was separated by centrifugation. Wallace et al. do not teach separation by means of an agitator blade of a stirrer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to recognize that the separation of the acid-precipitate from the plasma fraction can be

carried out by any acceptable means known in the art, including the blade of a stirrer, since techniques for separating a precipitate from a solution are routine in the art (claim 7).

Applicant's remarks regarding Wallace et al. has been considered but are not found to be persuasive. The reasons for maintaining the Wallace et al. and Newman et al. reference are the same as noted above.

Applicant does not dispute that it would have been well-known at the time of the invention to substitute centrifugation as taught by Wallace with using an agitator blade of a stirrer as a method of removing the precipitate and there is no evidence of record to suggest otherwise. As such, the rejection is maintained for the reasons of record and the reasons set forth above.

Claims 15, 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. (US 4341764; previously cited) in view of Newman et al. (US 5710254; previously cited) in view of Burnouf-Radosevich et al. (US 5408039; previously cited). The teachings of Wallace et al. in view of Newman et al. are outlined above. Wallace et al. in view of Newman et al. do not teach purification steps of the cryoprecipitated plasma fraction or vWF.

Burnouf-Radosevich et al. disclose a process for purifying human von Willebrand factor (vWF) from a cryoprecipitated plasma fraction, which comprises a series of purification steps (col. 5-7). Burnouf-Radosevich et al. disclose aluminum hydroxide treatment to remove fibronectin (col. 5 lines 43-49), a solvent-detergent treatment to destroy lipid enveloped viruses (col. 5 lines 57-60), and an anion exchange chromatographic step (col. 6). After the anion

exchange chromatographic step, Burnouf-Radosevich et al. disclose that the vWF eluate reveals a slight contamination by fibronectin (col. 6 lines 66-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Wallace et al. in view of Newman et al. by substituting the purification steps of Burnouf-Radosevich et al. to a plasma fraction for the separation of fibronectin and a coagulation factor (vWF) (claims 15, 17). The motivation to do so is given by Burnouf-Radosevich et al., which discloses further purification steps of plasma fraction in the separation of fibronectin and a different coagulation factor than that of Wallace et al. (i.e. vWF). It would be reasonable for one of ordinary skill to recognize that additional purification steps of Burnouf-Radosevich et al. would yield a purer protein product and that since Wallace et al. already disclose the separation of a coagulation factor; a specific factor (i.e. vWF) can therefore be separated.

Applicant's remarks regarding the Wallace et al. has been considered but are not found to be persuasive.

The reasons for maintaining the Wallace et al. reference and Newman et al. reference are the same as noted above.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maryam Monshipouri/

Primary Examiner, Art Unit 1656

April 21, 2010

M. Tsay
Art Unit 1656